DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 23, 2010 has been entered.

Claims 1-37, 48-50 are cancelled. Claim 45 is withdrawn. Claims 51, 52 are new. With regard to claim 45, it is noted that a withdrawn claim must include the text of the claim. Applicant must comply with 37 CFR 1.121 or risk non-entry of the claims.

Claims 38-44, 46-47, 51, 52, drawn to an expression vector comprising a nucleic acid sequence of CAP(6D)-1,2 and human B7.1, are under consideration.

Maintained Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 38-44, 46, 47 remain rejected and new claims 51, 52 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Schlom et al., US Patent 6,045,802, in view of Matteucci, US Patent 4,923,808, patented May 8, 1990, Horig et al., 2000, Cancer Immunol. Immunother. 49: 504-514, Parmiani et al., 2002, J. Natl. Cancer Inst., 94: 805-818, for reasons of record, June 10, 2009, February 23, 2010.

The rejection of June 10, 2009 is copied below for Applicant's convenience.

Schlom et al. teach a recombinant virus which has incorporated into its genome a gene encoding an antigen to a disease causing agent and a recombinant virus which has incorporated into its genome a gene encoding an immunostimulatory molecule(s) for the purpose of stimulating an immune response against the disease causing agent (Schlom et al., abstract). Schlom et al. teach that several antigens are identified for use in recombinant vaccines for cancer therapies. One such antigen is human carcinoembryonic antigen (CEA) (Schlom et al., col. 2, lines 55-57). With regard to an immunostimulatory molecule, Schlom et al. teach the expression of the B7 gene family (Schlom et al., col. 3, 4th parag.). One B7 family member is B7.1 (Schlom et al. col. 7, line 46).

While Schlom et al. teach expression of CEA and B7.1 in a cancer vaccine, Schlom et al. do not teach SEQ ID NO. 6, a nucleic acid that encodes wild type human CEA protein.

Matteucci teaches that nucleic acids can comprise silent mutations and produce proteins at high yields (Matteucci, col. 2, 2nd parag.). Matteucci teaches that silent mutations are those in which a nucleotide change is not expressed as an amino acid change because of the degeneracy of the genetic code, while expressed mutations appear as changes in the amino acid sequence (Matteucci, col. 4, lines 1-5). Matteucci teaches that silent mutations are introduced in order to select for host organism codon preference, to remove bases which, when transcribed as mRNA would pair with other mRNA bases to form stem and loop structures that impede translation, or to achieve enhanced expression in other ways for which no theoretical basis has yet been

advanced (Matteucci, col. 5, 1st parag.). It is noted that while Matteucci's title of the invention is to increasing secretion of secreted proteins, Matteucci teaches that silent mutations act beneficially at the level of expression, rather than at the level of secretion (Matteucci, col. 5, lines 8-9). As such, Mateucci's teaching is not limited to translation of secreted proteins.

All of the component parts are taught by Schlom et al. and Matteucci. The only difference is the combination of the "old elements" into a single expression system comprising SEQ ID NO. 6 and a nucleic acid sequence encoding human B7.1. It would have been obvious for an artisan to take the wild type nucleic acid sequence of human CEA and to make silent mutations in the sequence. An artisan would have done so because Matteucci teaches that making silent mutations in a nucleic acid sequence increases the translation of protein.

It is noted that while Schlom et al. provide a working example of expressing CEA and B7 from separate vectors (see Examples 3-7), Schlom et al. teach that the genes can be inserted into one recombinant vector (Schlom et al., col. 1, under Field of the Invention)

With regard to the claims being drawn to viral vectors (claims 40-43), Schlom et al. teach that a number of viral vectors (including fowlpox virus) can be used (Schlom et al., col. 8, 2nd parag. under Virus Vectors). With regard to ALVAC vectors, the art at the time of filing teaches that artisan were actively using ALVAC vectors to express human CEA and B7.1 co-stimulatory molecule (e.g. see Horig et al.). As such, use of any viral vector, including that of ALVAC is a matter of design choice.

With regard to the claims being drawn to the vector further comprising one additional tumor associated antigen, it is noted that Schlom et al. teach that the vector can express one or more antigens (Schlom et al., col., 1, line 19). The art recognizes that additional epitopes can be expressed from the vector as Parmiani et al., teach that human and animal tumors express multiple tumor-associated antigen (TAA) epitopes that are recognized by T cells and that some of the TAA epitopes can be lost or expressed at different times during tumor growth. As such, a vaccine against multiple TAA epitopes is more effective than a vaccine against a single epitope (Parmiani et al., page 808, 1st col., parag. under Single Epitope versus Polyepitope Vaccines). Given this teaching, an artisan would also include a second nucleic acid sequence encoding a

tumor-associated antigen in order to generate an immune response to tumor cells when a particular epitope is expressed during a particular stage of tumor growth.

Applicant's arguments filed August 23, 2010 have been fully considered but they are not persuasive.

Applicant indicates that the Office Action indicates that Schlom teaches the use of CEA (but not Applicant's SEQ ID NO. 6) and B7 in a cancer vaccine and that Matteucci teaches the use of silent mutations to change the nucleotide sequence that encode a protein without changing the amino acid sequence to provide improved protein production. Applicant indicates that this line of reasoning cannot support a prima facie case of obviousness. Applicant indicates that the line of reasoning is completely contrary to Pharmastem. Matteucci provides general guidance as to how to modify nucleic acid sequences and a limited number of specific examples of modified nucleic acid sequences. None of the cited references provide any guidance to arrive at SEQ ID NO. 6; Matteucci provides no guidance to which particular nucleotides should be modified (Applicant's response, pages 3-4). In response, Matteucci teaches that silent mutations can be made in a nucleic acid sequence and that making these silent mutations is routine in the art. Given Matteucci's teaching, it is also routine in the art to express the nucleic acids comprising silent mutations in them and isolate those that exhibit increased protein expression. Matteucci is not relied upon for teaching specific sequences or structures within a nucleic acid sequence that would be of interest to change; rather Matteucci teaches that silent mutations can be made and that one advantage of making silent mutations is that some sequences exhibit higher protein expression. With regard to Applicant referring

to Pharmastem, it is unclear what about Pharmastem the rejection is contrary to. The Examiner has looked up Pharmastem and has found Pharmastem Therapeutics, Inc. v. Viacell, Inc., 491 F.3d 1342 (Fed. Cir. 2007), which in addition to being an infringement case, was a case where the claims were invalid as obvious since prior art inferred presence of stem cells in cord blood. Applicant's reference to Pharmastem is unclear because the case has nothing to do with obviousness of silent mutations. Alternatively, in line with the invalidation of the patent, wherein the prior art inferred presence of stem cells in cord blood, analogously, Matteucci teaches that silent mutations in a sequence can be made. One such silent mutation, while not specifically disclosed, is inferred from Matteucci's teaching.

Applicant refers to MPEP 2141 and indicates that the Office Action has not provided any clear reasoning supporting the rejections as required by MPEP 2143 and has merely provided conclusions (Applicant" response, pages 4-5). In response, this is not persuasive. The Examiner relied on "exemplary rationales," including "simple substitution," where silent mutations are changes in the wild type sequence nucleic acid sequence, wherein the changes in nucleic acid sequence do not change the sequence of the protein sequence; "use of a known technique to improve similar methods in the same way," wherein Matteucci teaches that silent mutations in nucleic acid sequences encoding proteins can improve protein expression levels, and "some teaching, suggestion, or motivation in the prior art to modify or combine prior art teachings to arrive at the claimed

invention," wherein Matteucci teach that silent mutations in nucleic acid sequences can be used to increase protein expression levels.

Applicant indicates that "combining prior art elements according to known methods to yield predictable results" and "simple substitution" were not engaged because the elements of the claimed subject matter did not exist. Wild type CEA, nucleotides A, T, G, and C and Matteuchi's method were known in the art, but SEQ ID NO. 6 was not. Further, Applicant's sequence contains 246 nucleotide substitutions were not known (Applicant's response, page 5). In response, this is not persuasive. With regard to Applicant indicating that SEQ ID NO. 6 was not specifically known, Matteucci teaches an artisan how to obtain nucleic acid sequences comprising silent mutations. While there is a large number of nucleic acid substitutions from the wild type sequence to that of SEQ ID NO. 6, it is well within the ability of an artisan to generate sequences comprising silent mutations.

With regard to Applicant indicating that the Action has not shown that the claimed subject matter is simply a "base" product that has been improved in the same manner as a "comparable" product as the Action does not describe any "comparable" product (Applicant's response, page 5), the Action has indicated that the wild type sequence of CEA was known (Schlom et al.) and that Matteucci teaches how to make silent mutations in a wild type sequence wherein the mutated nucleic acid sequence encodes wild type protein. Matteucci also teaches that artisans make silent mutations in nucleic acid sequences because sequences with silent mutations have been shown to exhibit increased protein

expression. As such, the increased protein expression resulting from the silent mutation is the improvement over the base product.

With regard to Applicant indicating that applying a known technique to a known device (method or product) is inapplicable (Applicant's response, page 6), an artisan would have recognized that the known technique would have yielded predictable results and resulted in an improved system (Applicant's response, page 6). In response, as indicated above, Matteucci teach that silent mutations can be made and that silent mutations in a nucleic acid sequence lead to increase protein expression.

With regard to "obvious to try," Applicant indicates that it has not been shown that SEQ ID NO. 6 resulted from a finite number of predictable solutions (Applicant's response, page 6). In response, this is not persuasive. An artisan would understand that while the number of possible silent mutations can be made within a nucleic acid sequence is large, the sequence itself is a finite number (2269 nucleotides) and that there are only certain mutations that can be made within a triplet of nucleotides that encode the same amino acid. As such, "obvious to try" can also be a rationale used to combine Schlom and Matteucci.

With regard to Applicant referring to "teaching, suggestion, or motivation," Applicant indicates that the Action does not provide any reason why an artisan would have taken the wild type sequence and made silent mutations and identified sequences that resulted in higher CEA protein expression (Applicant's response, page 7). In response, it is routine in the art for an artisan to improve protein expression from a expression vector. In the instant case, an artisan

would want to express more CAP(6D)-1,2, a cancer cell antigen, in order to have more antigen to present to the immune system.

With regard to Applicant indicating exemplary rationale F (Applicant's response, pages 5-6); Applicant is correct that this is a less likely rationale used to combine the teachings of Schlom and Matteucci.

Thus, the claims remain rejected.

Conclusion

No claims allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama whose telephone number is 571-272-2911. The examiner can normally be reached Mondays, Wednesdays, Thursdays, and Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Joanne Hama/
Primary Examiner
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